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Dynamic kinetic resolution of secondary aromatic alcohols with new efficient acyl donors

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ABSTRACT

A new and efficient dynamic kinetic resolution (DKR) process of secondary aromatic alcohols by using long carbon-chain esters as acyl donors has been developed. During the process, the transesterification catalyzed by CD8604 was found to be the main reason for the decrease in enantiomeric excess (ee). Using complex acyl donors, such as 4-chlorophenyl valerate, we could effectively inhibit the resin-catalyzed transesterification, and an excellent ee value (>99%) at high yield (>99%) was achieved. The mechanism for the inhibition of resin-catalyzed transesterification is believed to be the formation of micro-micelles in the pores of CD8604. It is noteworthy that the system can be reused more than 20 times without a loss of yield or ee value.

1. Introduction

Dynamic kinetic resolution (DKR) provides an efficient method for preparing enantiomerically pure compounds. Dynamic kinetic resolution is a kinetic resolution coupled with an in situ racemization of slow-reacting substrate,[1,2] that could potentially surpass the main drawback of kinetic resolution,[3,4] increase the theoretical maximum yield from 50% to 100% and avoid separation of the unwanted enantiomer from the reaction system. According to previous studies, for an efficient chemo-enzymatic DKR of secondary alcohols, resolution and racemization catalysts are two indispensable requirements. Until now, there are several lipases that meet the requirements for the dynamic kinetic resolution (DKR) of secondary alcohols,[5–10] and only a few species of racemization catalysts have been reported to be applicable.[11] However, in these commonly used racemization catalysts, while the transition metal catalysts were commercially available and effective enough, they were expensive while acid zeolites were relatively ineffective. In our previous research, an acid resin, known as CD8604, was found to be very efficient in the DKR of secondary alcohols.[12] As a racemization catalyst, CD8604 was less expensive, less toxic, and more compatible with the enzymes,[13–19] although there were still some disadvantages in using it. During the DKR process of secondary alcohols, non-selective transesterification of the substrates catalyzed by CD8604 usually occurred as well, and thus the ee values of many products were not satisfactory enough. Herein, a further study about inhibiting the non-selective transesterification catalyzed by CD8604 is reported and the mechanism is studied. Also, a better DKR process was achieved and aromatic valerates of various secondary alcohols with excellent yield (>99) and high ee values (>99) were obtained. The same excellent results can be achieved when the system is used more than 20 times.

2. Result and discussion

In our previous study, CD8604 catalyzed non-selective transesterification of substrates was presumed to be the reason for the low ee value of the DKR of 1-phenylethanol. Similar to previous literature,[8,20,21] using complex acyl donors instead of common ones such as vinyl acetate and isopropyl acetate was an effective method to increase the selectivity of the DKR. However, this method helped us obtain an efficient DKR of some limited secondary alcohols. Firstly, the non-selective transesterification of 1-phenylethanol catalyzed by CD8604 with a different acyl donor was investigated and the results are shown in Table 1. It was found that

Table 1
Transesterification catalyzed by acid resin

Entry	Acyl donor	Yield (%)	Time (h)
1	Vinyl acetate	100	10
2	Isopropenyl acetate	100	10
3	Phenyl acetate	20.6	12
4	2-Chlorophenyl acetate	16.5	12
5	3-Chlorophenyl acetate	17.6	12
6	4-Chlorophenyl acetate	15.8	12
7	4-Methylphenyl acetate	14.0	12
8	4-Methoxybenzyl acetate	11.6	12

Reaction conditions: 1-phenylethanol, 100 mmol/L; toluene, 2 mL; donors, 300 mmol/L; temperature, 40 °C; rotation speed, 200r/min; CD8604, 20 mg/ml.

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all acyl donors used in previous studies could catalyze the non-selective transesterification of substrates, which coincided with our previous assumptions.[12] For example, if vinyl acetate, which had the fastest transesterification rate catalyzed by a resin (Table 1, entry 1), was chosen as the acyl donor, the ee value of the DKR was only 24.2%. However, when we used 4-chlorophenyl acetate with the lower rate of non-selective transesterification (Table 1, entry 6), the ee value of the DKR could reach 71.0%.

Since changing the alcohol moiety of the acyl donors would suppress the rate of non-selective transesterification, the same results could also be achieved if the acyl moiety of the acyl donors were changed. In the reaction of DKR, 4-chlorophenyl acetate performed better than other acyl donors.[12] Therefore, a series of acyl donors were synthesized with 4-chlorophenyl as the alcohol moiety and different long carbon-chain acids as the acyl moiety for further study; the data are shown in Table 2.

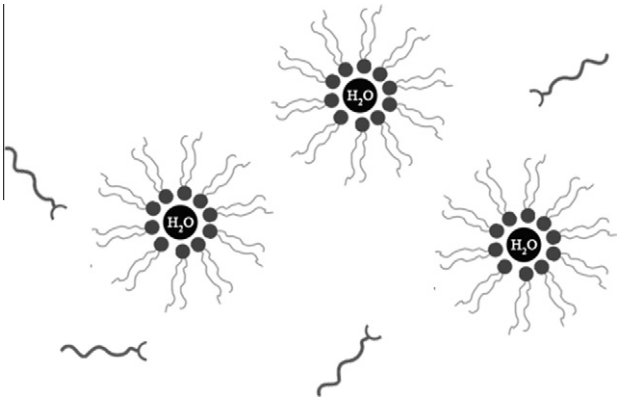


Figure 1. The micro-micelles in the pore of acid resin.

Table 2
Transesterification catalyzed by acid resin

Entry	Acyl donor	Yield (%)	Time (h)
1	4-Chlorophenyl acetate	15.8	12
2	4-Chlorophenyl propionate	12.9	12
3	4-Chlorophenyl butyrate	5.12	12
4	4-Chlorophenyl valerate	0	18
5	4-Chlorophenyl caproate	0	18
6	4-Chlorophenyl enanthate	0	18
7	4-Chlorophenyl caprylate	0	18
8*	4-Chlorophenyl valerate	8.24	20

Reaction conditions: 1-Phenylethanol, 100 mmol/L; donors, 300 mmol/L; temperature, 40 °C; rotation speed, 200 r/min; toluene, 2 mL.
Entries 1–7—CD8604 (moisture: 40%), 20 mg/ml.
Entry 8*—CD8604 (moisture: ~5%) was dried for 7 days at 7 Pa and 80 °C.

As expected, when the carbon chain of the acyl donor became longer, the rate of transesterification catalyzed by the resin became lower. Non-selective transesterification was almost completely inhibited when the number of acyl carbon atoms was over five (Table 2, entries 4–7).

There may be two main reasons for the inhibition of the long carbon-chain esters in the transesterification reaction catalyzed by the resin. One is the steric effect of the substrates, since the complex structures would make the active site more difficult to reach. The second reason is the moisture of the resin catalytic environment. The resin has the ability to retain water inside its pores, thus creating a microenvironment with a high water content (40%). This is a good environment that favors the formation of micro-micelles, when the long-chain donors are placed into the aperture (Fig. 1). Due to the formation of micro-micelles, long-chain acyl donors are locally enriched. Consequently, without enough reactive sites of the acyl donor, secondary alcohols can be subjected to a racemization reaction rather than the transesterification. This proposal might be explained by a designed experiment (Table 2, entry 8*). If CD8604 was dried as shown, the micro-micelles were unable to form due to the loss of most of its moisture. Therefore, secondary alcohols were able to react with the acyl donor and non-selective transesterification took place.

Complex acyl donors could inhibit the transesterification reaction effectively, and the enzymatic reaction was almost unaffected when these esters were used as acyl donors in the kinetic resolution (Table 3). The results of the experiment are shown in Table 3. It can be seen that all of the kinetic resolutions achieved 50% yield in 0.5 h with high ee values of the products.

Encouraged by these results, we used these esters as acyl donors in the dynamic kinetic resolution of 1-phenylethanol. As expected, the results of the DKRs were greatly improved while the non-selective transesterification reaction was suppressed (Table 4).

Table 3
The kinetic resolution of 1-phenylethanol with different acyl donors

Entry	Acyl donor	ee_p (%)	Yield (%)	Time (min)
1	4-Chlorophenyl acetate	>99	50	30
2	4-Chlorophenyl propionate	>99	50	30
3	4-Chlorophenyl butyrate	>99	50	30
4	4-Chlorophenyl valerate	>99	50	30
5	4-Chlorophenyl caproate	>99	50	30
6	4-Chlorophenyl enanthate	>99	50	30
7	4-Chlorophenyl caprylate	>99	50	30

Reaction conditions: 1-Phenylethanol, 100 mmol/L; toluene, 2 mL; donors, 300 mmol/L; temperature, 40 °C; rotation speed, 200 r/min; Novozyme 435, 10 mg/ml.

This was encouraging since the yield and ee of DKRs were nearly 100% when we used long carbon-chain acyl donors, such as 4-chlorophenyl valerate and so on (Table 4, entries 5–8).

Table 4
The DKR of 1-phenylethanol with different acyl donors

Entry	Acyl donor	ee_p (%)	Yield (%)	Time (h)
1	4-Methylphenyl acetate	96.1	57.8	24
2	4-Chlorophenyl acetate	70.9	92.4	6
3	4-Chlorophenyl propionate	86.2	>99	6
4	4-Chlorophenyl butyrate	92.1	>99	6
5	4-Chlorophenyl valerate	>99	>99	6
6	4-Chlorophenyl caproate	>99	>99	6
7	4-Chlorophenyl enanthate	>99	>99	6
8	4-Chlorophenyl caprylate	>99	>99	6

Reaction conditions: 1-phenylethanol, 100 mmol/L; donors, 300 mmol/L; temperature, 40 °C; rotation speed, 200 r/min; Novozyme 435, 10 mg/ml; CD8604, 20 mg/ml, toluene, 2 mL.

Since 4-chlorophenyl valerate performed very well as an acyl donor in the DKR of 1-phenylethanol, it was thus employed in the DKR of other secondary alcohols. The results are summarized in Table 5.

It is noteworthy that 4-chlorophenyl valerate gave good results an acyl donor in the DKRs of secondary alcohols. Most of the reactions achieved nearly 100% ee at 100% yield. The reaction also proceeded quicker when electro-donating groups were substituted on the benzene ring. However, when the substituents were electron-withdrawing groups, the rate of reaction decreased.

In order to investigate the reusability of the resin-lipase coupled catalysis system, the repeated use of CD8604 and Novozym435 in the DKR of *rac*-1-phenylethanol with 4-chlorophenyl valerate as an acyl donor was studied.

As shown in Figure 2, after 20 cycles, the ee was almost unchanged, while the yields remained nearly the same (>99%). Thus,

Table 5
The DKR of secondary alcohols with 4-chlorophenyl valerate as the acyl donor

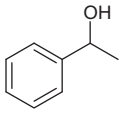
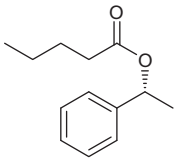
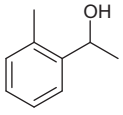
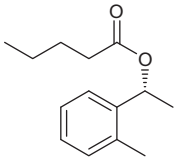
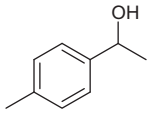
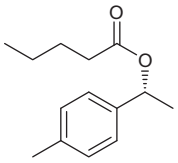
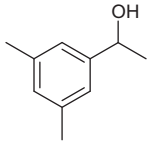
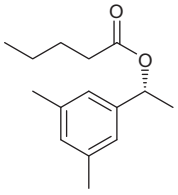
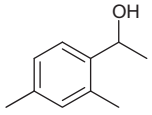
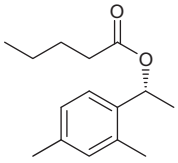
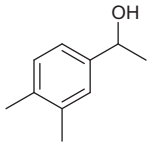
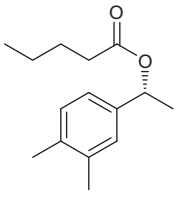
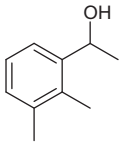
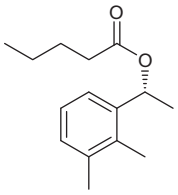
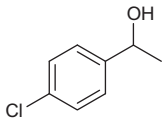
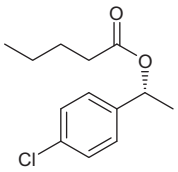
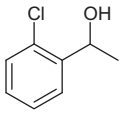
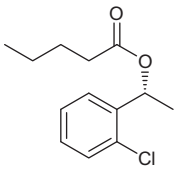
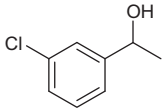
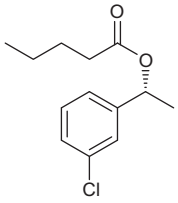
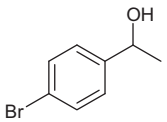
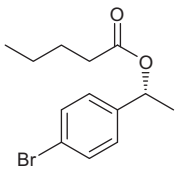
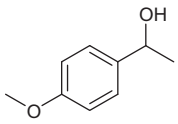
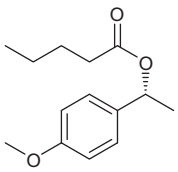
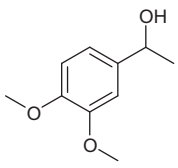
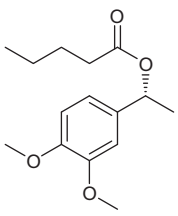
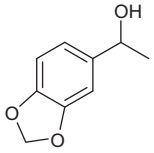
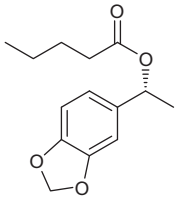
Entry	Substrate	Product	ee (%)	Yield (%)
1 (**5a**)			>99	>99
2 (**5b**)			>99	>99
3 (**5c**)			>99	>99
4 (**5d**)			>99	>99
5 (**5e**)			>99	>99
6 (**5f**)			>99	>99
7 (**5g**)			>99	>99
8 (**5h**)			>99	95.6
9 (**5i**)			>99	>99

Table 5 (*continued*)

Entry	Substrate	Product	ee (%)	Yield (%)
10 (**5j**)			>99	>99
11 (**5k**)			>99	>99
12 (**5l**)			>99	>99
13 (**5m**)			>99	>99
14 (**5n**)			>99	>99

Reaction conditions: alcohols, 100 mmol/L; donors, 300 mmol/L; CD8604, 20 mg/ml, temperature, 40 °C; rotation speed, 200 r/min; Novozyme 435, 10 mg/ml; toluene, 2 mL.

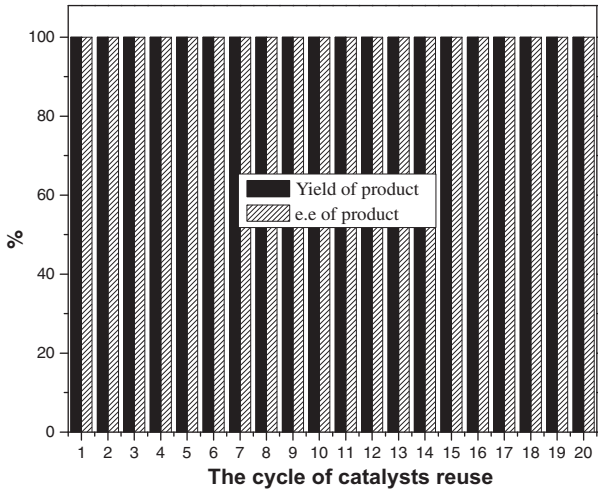


Figure 2. The catalyst reuse with 4-chlorophenyl valerate as the acyl donor.

4-chlorophenyl valerate is an excellent donor in the DKR of secondary alcohols.

3. Conclusion

In conclusion, a highly efficient DKR of secondary aromatic alcohols using long carbon-chain esters as acyl donors has been developed. During the process, the transesterification catalyzed by CD8604 was found as the main reason for the decrease in ee. Using complex acyl donors inhibited the resin-catalyzed transesterification, and excellent ee values (>99%) and high yields (>99%) were achieved. The mechanism for the inhibition of resin-catalyzed transesterification might be the formation of micro-micelles in the pores of CD8604. It is noteworthy that this reaction system has been proven to be applicable for many substrates and also showed good stability. It can also be reused for more than 20 times without a loss of yield or ee.

4. Experimental

4.1. General

All substrates and acyl donors were synthesized, except for 1-phenylethanol, which is a product from Aladdin. Lipase Novozyme 435 was obtained from Novozymes and CD8604 was obtained from Hangzhou Zhengguang resin Co., Ltd.

The results of the reactions were detected by GC (Fuli 9790) on a CP-CYCLODEXTRIN β-2,3,6-M-19, FS 50X.25(.25) chiral column with FID detection. ^{1}H and ^{13}C NMR spectra were recorded on a Varian MercuryVx 400 spectrometer (400 MHz) using $CDCl_3$ as the solvent.

4.2. General procedure for the non-selective transesterification reaction

At first, *rac*-1-phenylethanol (24.4 mg, 200 mmol) and CD8604 (40 mg) were dissolved in toluene (2 mL). The acyl donors (600 mmol) were then added into the mixture system, and the system stirred at 40 °C.

4.3. Kinetic resolution of 1-phenylethanol

In a typical kinetic resolution, the acyl donor (600 mmol) was added to a stirred solution of *rac*-1-phenylethanol (24.4 mg, 200 mmol) and lipase Novozyme 435 (20 mg) in toluene (2 ml) at 40 °C.

4.4. Dynamic kinetic resolution of 1-phenylethanol

The reaction consisted of *rac*-1-phenylethanol (24.4 mg, 200 mmol), lipase Novozyme 435 (20 mg), acid resin CD8604 (40 mg) and acyl donor (600 mmol). After all the materials were dissolved in toluene (2 mL), the solvent was stirred at 40 °C.

4.5. General procedure for the dynamic kinetic resolution of secondary alcohols

The *rac*-alcohol (200 mmol) and acid resin CD8604 (40 mg) were dissolved in toluene (2 mL). The mixture was stirred at 40 °C after which lipase Novozyme 435 (20 mg) and acyl donor 4-chlorophenyl valerate (600 mmol) were added.

4.6. Spectroscopic data for all the compounds

4.6.1. 1-Phenylethanol valerate 5a

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) 0.94 (t, J = 7.6 Hz, 3H; CH_3), 1.38 (m, J = 7.6 Hz, 2H; CH_2), 1.56 (d, J = 6.4 Hz, 3H; CH_3), 1.65 (m, J = 7.6 Hz, 2H; CH_2), 2.3 (t, J = 7.6 Hz, 2H; CH_2), 5.92 (m, J = 6.4 Hz, H; CH), 7.31 (t, H; Ph-H), 7.37 (d, J = 3.6 Hz, 4H; Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.62, 22.14 (CH_3), 22.18, 26.94, 34.24 (CH_2), 71.92 (CH), 125.96, 127.69, 128.37, 141.78 (Ph), 172.98 (CO). EI-MS (70 eV): m/z (%) 206 (35), 122 (100), 104 (100), 77 (60), 57 (31), 41 (15), 29 (12). IR absorption bands (cm^{-1}): 3303 (w), 2960 (s), 2932 (s), 2870 (m), 1736 (vs), 1495 (w), 1454 (n), 1374 (n), 1250 (s), 1174 (s), 1063 (s), 1029 (m), 940 (w), 758 (m), 698 (m), 539 (w). $[\alpha]_D^{25} = +69.1$ (c 1.00, CH_2Cl_2).

4.6.2. 1-(2-Methylphenyl)ethanol valerate 5b

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) 0.95 (t, J = 7.2 Hz, 3H; CH_3), 1.39 (m, J = 7.2 Hz, 2H; CH_2), 1.54 (d, J = 6.8 Hz, 3H; CH_3), 1.66 (m, J = 7.2 Hz, 2H; CH_2), 2.38 (t, J = 5.6 Hz, 2H; CH_2), 2.4 (s, 3H; CH_3), 6.14 (m, J = 6.4 Hz, H; CH), 7.24 (m, J = 8.0 Hz, 3H; Ph-H), 7.43 (d, J = 6.8 Hz, H; Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.64, 18.94, 21.31 (CH_3), 22.16, 26.95, 34.21 (CH_2), 68.84 (CH), 125.15, 126.15, 127.47, 130.31, 134.62, 140.16 (Ph), 172.98 (CO). EI-MS (70 eV): m/z (%) 118 (100), 91 (30), 77 (10), 57 (12), 41 (10), 29 (10). IR absorption bands (cm^{-1}): 2960(s), 2931 (s), 2870 (m), 1735 (s), 1491 (w), 1459 (m), 1374 (m), 1252 (m), 1175 (s), 1090 (m), 1064 (s), 1001 (w), 941 (w), 758(m), 726(w), 459(w). $[\alpha]_D^{25} = +62.4$ (c 1.00, CH_2Cl_2).

4.6.3. 1-(4-Methylphenyl)ethanol valerate 5c

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) 0.94 (t, J = 8.0 Hz, 3H; CH_3), 1.36 (m, J = 7.2 Hz, 2H; CH_2), 1.56 (d, J = 6.4 Hz, 3H; CH_3), 1.65 (m, J = 8.0 Hz, 2H; CH_2), 2.34 (t, J = 1.2 Hz, 2H; CH_2), 2.36 (s, 3H; CH_3), 5.90 (m, J = 6.8 Hz, H; CH), 7.19 (d, J = 8.0 Hz, 2H; Ph-H), 7.28 (d, J = 8.0 Hz, 2H; Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.63, 21.03, 22.16 (CH_3), 22.10, 26.97, 34.28 (CH_2), 71.85 (CH), 126.00, 129.06, 137.41, 138.83 (Ph), 173.00 (CO). EI-MS (70 eV): m/z (%) 220 (75), 136 (100), 117 (100), 103 (27), 91 (87), 77 (25), 57 (38), 41 (25), 29 (15). IR absorption bands (cm^{-1}): 2960 (s), 2931 (s), 2870 (s), 1735 (vs), 1614 (w), 1517 (m), 1455 (m), 1374 (m), 1250 (s), 1173 (vs), 1094 (m), 1062 (s), 1021 (m), 1012 (m), 941 (m), 860 (w), 815 (s), 727 (w), 541 (m). $[\alpha]_D^{25} = +71.3$ (c 1.00, CH_2Cl_2).

4.6.4. 1-(3,5-Dimethylphenyl)ethanol valerate 5d

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) 0.95 (t, J = 7.2 Hz, 3H; CH_3), 1.39 (m, J = 8.0 Hz, 2H; CH_2), 1.52 (d, J = 6.0 Hz, 3H; CH_3), 1.66 (m, J = 7.6 Hz, 2H; CH_2), 2.27 (t, J = 5.2 Hz, 2H; CH_2), 2.35 (s, 6H; CH_3), 6.10 (m, J = 6.0 Hz, H; CH), 7.04 (m, J = 8.8 Hz, 2H; Ph-H), 7.22 (s, H; Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.66, 18.48, 21.30, 22.16 (CH_3), 21.03, 26.99, 34.23 (CH_2), 68.99 (CH), 125.86, 128.21, 130.26, 131.26, 135.53, 139.85 (Ph), 172.99 (CO). EI-MS (70 eV): m/z (%) 150 (12), 133 (100), 117 (100), 105 (30), 91 (30), 77 (15), 57 (15), 41 (12), 29 (10). IR absorption bands (cm^{-1}): 2960 (s), 2926 (s), 2869 (m), 1735 (vs), 1503 (m), 1457 (m), 1373 (m), 1249 (s), 1176 (s), 1089 (m), 1063(s), 1026(m), 941 (w), 889 (w), 811 (m), 468 (m). $[\alpha]_D^{25} = +47.8$ (c 1.00, CH_2Cl_2).

4.6.5. 1-(2,4-Dimethylphenyl)ethanol valerate 5e

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) 0.94 (t, J = 7.2 Hz, 3H; CH_3), 1.36 (m, J = 7.6 Hz, 2H; CH_2), 1.52 (d, J = 6.8 Hz, 3H; CH_3), 1.65 (m, J = 8.0 Hz, 2H; CH_2), 2.25 (t, J = 4.8 Hz, 2H; CH_2), 2.32 (s, H; CH_3), 2.36 (s, H; CH_3), 6.10 (m, J = 6.0 Hz, H; CH), 6.99 (s, H; Ph-H), 7.05 (d, J = 8.0 Hz, H; Ph-H), 7.31 (d, J = 8.0 Hz, H; Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.63, 18.87, 22.11, 22.16 (CH_3), 20.89, 26.95, 34.23 (CH_2), 68.87 (CH), 125.23, 126.82, 126.90, 131.09, 134.59, 137.13 (Ph), 173.04 (CO). EI-MS (70 eV): m/z (%) 150 (5), 132 (100), 117 (50), 105 (18), 91 (20), 77 (10), 57 (10), 41 (10), 29 (8). IR absorption bands (cm^{-1}): 3426 (w), 2957 (s), 2921 (vs), 2852 (s), 1735 (s), 1607 (w), 1508 (w), 1460 (m), 1375 (m), 1254 (m), 1175 (s), 1091 (w), 1060 (s), 942 (w), 819 (w), 737 (m). $[\alpha]_D^{25} = +43.2$ (c 1.00, CH_2Cl_2).

4.6.6. 1-(3,4-Dimethylphenyl)ethanol valerate 5f

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.92 (t, J = 7.2 Hz, 3H, CH_3), 1.34 (m, J = 7.2 Hz, 2H, CH_2), 1.54 (d, J = 6.4 Hz, 3H, CH_3), 1.63 (t, J = 7.6 Hz, 2H, CH_2), 2.28 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 2.33 (t, J = 8.0 Hz, 2H, CH_2), 5.87 (m, J = 6.4 Hz, 1H, CH), 7.13 (d, J = 7.2 Hz, 2H, Ph-H), 7.16 (s, H, Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.66, 19.39, 19.75 (CH_3), 22.14, 26.98, 34.31 (CH_2), 71.92 (CH), 123.42, 127.39, 129.65, 136.10, 136.54, 139.27 (Ph), 173.05 (CO). EI-MS (70 eV): m/z (%) 234 (80), 150 (100), 135 (100), 117 (100), 105 (50), 91 (55), 77 (25), 57 (38), 41 (25), 29 (16). IR absorption bands (cm^{-1}): 2960 (s), 2931 (s), 2869 (m), 1735 (vs), 1505 (w), 1453 (m), 1374 (m), 1248 (m), 1175 (s), 1065 (m), 1020 (m), 943 (w), 819 (m), 721 (w). $[\alpha]_D^{25} = +50.2$ (c 1.00, CH_2Cl_2).

4.6.7. 1-(2,3-Dimethylphenyl)ethanol valerate 5g

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.94 (t, J = 7.2 Hz, 3H, CH_3), 1.36 (m, J = 7.2 Hz, 2H, CH_2), 1.56 (d, J = 6.4 Hz, 3H, CH_3), 1.65 (t, J = 7.6 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.37 (t, J = 8.0 Hz, 2H, CH_2), 5.89 (m, J = 6.4 Hz, 1H, CH), 1.16 (m, 3H, Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.66, 19.39, 19.75 (CH_3), 22,14, 26.98, 34.31 (CH_2), 71.92 (CH), 123.42, 127.39, 129.65, 136.10, 136.54, 139.27 (Ph), 173.05 (CO). EI-MS (70 eV): m/z (%) 234 (80), 150 (100), 135 (100), 117 (100), 105 (50), 91 (55), 77 (25), 57 (38), 4 1 (25), 29 (16). IR absorption bands (cm^{-1}): 2960 (s), 2931 (s), 2869 (m), 1735 (vs), 1505 (w), 1453 (m), 1374 (m), 1248 (m), 1175 (s), 1065 (m), 1020 (m), 943 (w), 819 (m), 721 (w). $[\alpha]_D^{25} = +44.3$ (c 1.00, CH_2Cl_2).

4.6.8. 1-(4-Chlorophenyl)ethanol valerate 5h

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) 0.93 (t, J = 7.6 Hz, 3H; CH_3), 1.36 (m, J = 7.6 Hz, 2H; CH_2), 1.52 (d, J = 6.4 Hz, 3H; CH_3), 1.65 (m, J = 7.6 Hz, 2H; CH_2), 2.35 (t, J = 6.4 Hz, 2H; CH_2), 5.88 (m, J = 6.4 Hz, H; CH), 7.30 (d, J = 8.0 Hz, 2H; Ph-H), 7.34 (d, J = 9.2 Hz, 2H; Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.59, 22.11 (CH_3), 22.11, 26.87, 34.16 (CH_2), 71.19 (CH), 127.38, 128.55, 133.43, 140.32 (Ph), 172.86 (CO). EI-MS (70 eV): m/z (%) 240 (38), 156 (100), 138 (100), 103 (100), 85 (62), 57 (40), 41 (20), 29 (15). IR absorption bands (cm^{-1}): 3450 (w), 2960 (s), 2932 (s), 2870 (m), 1737 (vs), 1598 (w), 1494 (s), 1457 (m), 1413 (m), 374 (m), 1249 (s), 1172 (s), 1092 (s), 1063 (s), 1014 (s), 941 (m), 827 (s), 789 (w), 539 (m). $[\alpha]_D^{25} = +69.1$ (c 1.00, CH_2Cl_2).

4.6.9. 1-(2-Chlorophenyl)ethanol valerate 5i

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) 0.94 (t, J = 7.2 Hz, 3H; CH_3), 1.39 (m, J = 7.6 Hz, 2H; CH_2), 1.54 (d, J = 6.4 Hz, 3H; CH_3), 1.66 (m, J = 7.2 Hz, 2H; CH_2), 2.39 (t, J = 7.2 Hz, 2H; CH_2), 6.26 (m, J = 6.4 Hz, H; CH), 7.24 (t, J = 7.6 Hz, H; Ph-H), 7.30 (t, J = 6.8 Hz, H; Ph-H), 7.36 (d, J = 8.0 Hz, H; Ph-H), 7.47 (d, J = 7.6 Hz, H; Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.62, 20.97 (CH_3), 22.14, 26.91, 34.09 (CH_2), 68.85 (CH), 126.42, 126.98, 128.61, 129.48, 131.87, 139.68 (Ph), 172.57 (CO). EI-MS (70 eV): m/z (%) 203 (90), 139 (100), 121 (62), 103 (75), 77 (38), 57 (18), 41 (10), 29 (10). IR absorption bands (cm^{-1}): 3068 (w), 2960 (s), 2932 (s), 2870 (m), 1740 (vs), 1472 (m), 1443 (m), 1373 (m), 1247 (s), 1173 (s), 1134 (m), 1075 (s), 1043 (s), 1006 (m), 943 (m), 755 (s), 693 (m), 462 (m). $[\alpha]_D^{25} = +41.3$ (c 1.00, CH_2Cl_2).

4.6.10. 1-(3-Chlorophenyl)ethanol valerate 5j

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) 0.93 (t, J = 7.6 Hz, 3H; CH_3), 1.37 (m, J = 7.2 Hz, 2H; CH_2), 1.52 (d, J = 6.4 Hz, 3H; CH_3), 1.66 (m, J = 7.6 Hz, 2H; CH_2), 2.36 (t, J = 7.6 Hz, 2H; CH_2), 5.87 (m, J = 6.4 Hz, H; CH), 7.23 (m, J = 3.2 Hz, 4H; Ph-H), 7.34 (s, H; Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.59, 22.11 (CH_3), 22.16, 26.89, 34.13 (CH_2), 71.16 (CH), 124.13, 126.06, 127.81, 129.69, 134.27, 143.86 (Ph), 172.84 (CO). EI-MS (70 eV): m/z (%) 240 (20), 156 (100), 139 (95), 103 (82), 77 (35), 57 (25), 41 (10), 29 (10). IR absorption bands (cm^{-1}): 3448 (w), 2960 (s), 2931 (s), 2870 (m), 1737 (vs), 1598 (w), 1575 (m), 1460 (m), 1374 (m), 1250 (m), 1171 (s), 1064 (s), 1013 (m), 941 (w), 882 (w), 826 (w), 786 (m), 694 (m). $[\alpha]_D^{25} = +63.3$ (c 1.00, CH_2Cl_2).

4.6.11. 1-(4-Bromophenyl)ethanol valerate 5k

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) 0.92 (t, J = 7.2 Hz, 3H; CH_3), 1.36 (m, J = 8.0 Hz, 2H; CH_2), 1.51 (d, J = 6.8 Hz, 3H; CH_3), 1.62 (m, J = 7.6 Hz, 2H; CH_2), 2.35 (t, J = 5.6 Hz, 2H; CH_2), 5.86 (m, J = 6.8 Hz, H; CH), 7.24 (d, J = 8.4 Hz, 2H; Ph-H), 7.48 (d, J = 8.8 Hz, 2H; Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.59, 22.07 (CH_3), 22.11, 26.89, 34.15 (CH_2), 71.23 (CH), 121.55, 127.71, 131.51, 140.83 (Ph), 172.85 (CO). EI-MS (70 eV): m/z (%) 284 (40), 202 (100), 182 (100), 157 (10), 104 (100), 85 (75), 77 (62), 57 (50), 41 (20), 29 (15). IR absorption bands (cm^{-1}): 3500 (w), 2959 (s), 2932 (s), 2869 (m), 1737 (vs), 1594 (w), 1490 (s), 1458 (m), 1410 (m), 1374 (m), 1248 (s), 1171 (s), 1068 (s), 1009 (s), 941 (m), 823 (s), 784 (w), 535(m). $[\alpha]_D^{25} = +63.5$ (c 1.00, CH_2Cl_2).

4.6.12. 1-(4-Methoxyphenyl)ethanol valerate 5l

^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ (ppm) 0.91 (t, J = 7.2 Hz, 3H; CH_3), 1.33 (m, J = 7.6 Hz, 2H; CH_2), 1.52 (d, J = 6.8 Hz, 3H; CH_3), 1.60 (m, J = 7.6 Hz, 2H; CH_2), 2.32 (t, J = 6.0 Hz, 2H; CH_2), 3.81 (s, 3H; CH_3), 5.88 (m, J = 6.8 Hz, H; CH), 6.90 (d, J = 8.8 Hz, 2H; Ph-H), 7.30 (d, J = 8.4 Hz, 2H; Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.61, 21.92 (CH_3), 22.12, 26.93, 34.28 (CH_2), 55.17 (OCH_3), 71.61 (CH), 113.70, 127.44, 133.84, 159.10 (Ph), 173.07 (CO). EI-MS (70 eV): m/z (%) 236 (45), 152 (12), 135 (100), 119 (43), 91(45), 77(12), 65(12), 57(10), 41 (10), 29 (8). IR absorption bands (cm^{-1}): 3450 (w), 2959 (vs), 2933 (vs), 2870 (s), 2838 (m), 1732 (vs), 1613 (s), 1586 (m), 1515 (vs), 1460 (s), 1374 (m), 1298 (s), 1248 (vs), 1174 (vs), 1093 (m), 1061 (s), 1035 (s), 1006 (m), 940 (m), 831 (s), 733 (w), 550 (m), 448 (w). $[\alpha]_D^{25} = +95.7$ (c 1.00, CH_2Cl_2).

4.6.13. 1-(3,4-Dimethoxyphenyl)ethanol valerate 5m

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.85 (t, J = 7.6 Hz, 3H, CH_3), 1.29 (m, J = 7.2 Hz, 2H, CH_2), 1.49 (d, J = 6.4 Hz, 3H, CH_3), 1.56 (m, J = 8.0 Hz, 2H, CH_2), 2.27 (t, J = 7.6 Hz, 2H, CH_2), 3.84 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 5.82 (m, J = 6.4 Hz, 1H, CH), 6.80 (m, 3H, Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.60, 21.97 (CH_3), 22,11, 26.94, 34.24 (CH_2), 55.73, 55.76 (OCH_3), 71.79 (CH), 109.37, 110.83, 118.43, 134.26, 148.52, 148.77 (Ph), 173.02 (CO). EI-MS (70 eV): m/z (%) 266 (100), 182 (100), 164 (100), 149 (80), 134 (20), 121 (40), 103 (30), 91 (40), 77 (37), 57 (25), 41 (20), 29 (15). IR absorption bands (cm^{-1}): 3445 (s), 2957 (vs), 2930 (vs), 2869 (s), 2837 (s), 1731 (vs), 1595 (s), 1515 (vs), 1460 (s), 1419 (s), 1370 (s), 1315 (s), 1259 (vs), 1164 (vs), 1103 (s), 1063 (s), 1028 (vs), 942 (m), 909 (m), 853 (m), 808 (s), 763 (m), 642 (m), 576 (w). $[\alpha]_D^{25} = +86.5$ (c 1.00, CH_2Cl_2).

4.6.14. 1-(3,4-Methylenedioxy)ethanol valerate 5n

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.87 (t, J = 7.6 Hz, 3H, CH_3), 1.29 (m, J = 7.2 Hz, 2H, CH_2), 1.48 (d, J = 6.8 Hz, 3H, CH_3), 1.57 (m, J = 7.6 Hz, 2H, CH_2), 2.28 (t, J = 7.6 Hz, 2H, CH_2), 5.79 (m, J = 6.8 Hz, 1H, CH), 5.93 (s, 2H, CH_2), 6.74 (m, 3H, Ph-H). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 13.61, 22.12 (CH_3), 22,14, 26.90, 34.24 (CH_2), 71.83 (CH), 100.96 (CH_2), 106.59, 108.02, 119.63, 135.68, 147.03, 147.62 (Ph), 173.04 (CO). EI-MS (70 eV): m/z (%) 166 (40), 166 (55), 149 (100), 119 (25), 91 (40), 77 (5), 66 (12), 57 (10), 41 (10), 29 (10). IR absorption bands (cm^{-1}): 3441 (m), 2960 (s), 2931 (s), 2873 (s), 2779 (w), 1733 (vs), 1609 (m), 1493 (s), 1445 (s), 1374 (s), 1322 (m), 1242 (vs), 1174 (s), 1135 (w), 1097 (m), 1040 (s), 937 (m), 911 (w), 859 (m), 811 (m), 761 (w), 726 (w), 636 (m), 558 (w). $[\alpha]_D^{25} = +64.6$ (c 1.00, CH_2Cl_2).

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